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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	McCart et al.
Appl. No.	:	09/991,721
Filed	:	November 13, 2001
For	:	COMBINED GROWTH FACTOR-DELETED AND THYMIDINE KINASE-DELETED VACCINIA VIRUS VECTOR
Examiner	:	Sullivan, Daniel M.
Group Art Unit	:	1636

DECLARATION UNDER 37 CFR 1.132 OF RICHARD C. CONDIT, PhD.

I, Richard C. Condit, Ph.D., do hereby declare:

1. I am currently Professor, Department of Molecular Genetics & Microbiology, University of Florida, Gainesville, FL, USA. A true and correct copy of my Curriculum Vitae is attached as Exhibit A.

2. I have authored or co-authored more than 60 scientific papers, including seminal research on replication of vaccinia virus. I serve on the Editorial Board of the Journal of Virology. I am an Associate Editor of Virology.

3. I earned my A.B. from University of California, Santa Cruz, my Ph.D. from Yale University, and completed postdoctoral fellowships at Imperial Cancer Research Fund and at SUNY, Stony Brook.

NOT OBVIOUS BASED ON COMPARISON WITH CLOSEST PRIOR ART

4. The invention, a combined thymidine kinase-deleted (TK-) and vaccinia growth factor-deleted (VGF-) vaccinia virus, would not have been obvious at the time of the May 1999 filing date, not even in view of the combination of the closest prior art, Buller et al., Nature 317: 813 (1985) and Buller et al., J Virol. 62: 866 (1988), not even on the reasoning that it would be desirable to combine the two safety mutations to achieve reduced virulence. Buller et al. 1985 describes a thymidine kinase-deleted (TK-) vaccinia virus. (I am the R. Condit acknowledged on

p. 814, col. 1, ¶ 2.) Buller et al. 1988 describes a vaccinia growth factor-deleted (VGF-) vaccinia virus.

5. There is more to this than just combining two SAFETY mutations. The actual mechanism of the mutations may be important, as reasoned in McCart et al., Cancer Res 61: 8751 (2001), which was published in December 2001 about two years after the May 1999 filing date. The authors provide a specific rationalization for use of both TK and VGF. Specifically, they reason that each of these mutations results in a virus that is specifically reduced in replication in resting cells, but not in dividing cells. Most of the cells in an animal are in a resting state, while tumor cells are actively dividing. Therefore a virus altered in this fashion would theoretically maintain competence for replication in tumor cells, thus killing them, while acquiring a reduced ability to replicate in resting cells, namely, in the remainder of the organism. This theory is original relative to the two Buller et al. papers. The mechanism proposed for TK is not mentioned in Buller et al. 1985, and the mechanism of VGF is considered but uncertain in Buller et al. 1988 on p. 872, col. 2, ¶ 1:

> "We found, as have others, that orthopoxvirus lesions in the brain lack focal hyperplasia, making it difficult to explain the higher virulence of the WT virus by growth-promoting activity of VGF."

This passage deals only with a theoretical mechanism of the VGF deletion and does not suggest tumor selectivity.

6. In neither case of Buller et al. 1985 nor Buller et al. 1988 is there any mention of tumor specificity.

7. There are many other possible "safety" mutations, as discussed in Tartaglia et al., Virology 188: 217 (1992), with many different mechanisms, including evasion of both the adaptive and innate immune response, control of host range, and other unknown mechanisms. While combinations of these safety mutations might result in reduced virulence, additivity is empirical. In Child et al., Virology 174: 625 (1990), a thymidine kinase-deleted and ribonucleotide reductase-deleted <u>double</u> deletion vaccinia virus was merely comparable in replication to the single deletion. In Tartaglia et al. 1992, only the deletion of <u>multiple</u> (18 ORFs

deleted to make NYVAC) virulence genes provided a highly attenuated effect. Thus a combined effect of a double deletion was speculative and could not have been predicted.

8. It is also worth noting that little in biology is predictable. The biological correlate of Murphy's law states that "Under carefully controlled environmental conditions, the organism does what it pleases." Tartaglia et al. 1992 states as much after discussing variance in reported virulence of similar TK mutants on p. 230, col. 1, line 3:

> "Such a finding again illustrates the multifactorial nature of virulence, in that varying effects can be observed using different virus genetic backgrounds and different animal model systems."

9. In short, it may be true that, knowing the prior art, one has the potential for hypothesizing a combination of virulence genes. Nevertheless, because of the quantity of virulence genes, there are a vast number of combinations. In the case of Paoletti et al. (1992) WO 92/15672, in which 38 ORFs were deleted to make NYVAC.2, there are a possibility of 703 double deletions. There was no motivation to select the TK and VGF ORFs because a prior art <u>double</u> deletion was not additive (Child et al. 1990) and only the deletion of <u>multiple</u> virulence genes provided a dramatic effect (Tartaglia et al. 1992). Therefore, given the enormous number of possibilities suggested by the prior art, and the failure of the prior art to suggest which of those possibilities is the claimed combination, the TK- and VGF- double deletion would <u>not</u> have been obvious.

PRIOR ART TEACHES AWAY

10. In the Childs et al. 1990 experiments, the thymidine kinase-deleted and ribonucleotide reductase-deleted vaccinia virus double deletion was not as attenuated as might have been predicted from the data with the two single deletions, and therefore this teaches away from the idea that the effects of combination of any two safety mutations is predictable and obvious. Indeed, I could find no examples of anyone making double deletion mutants in order to further attenuate vaccinia virus subsequent to the Childs et al 1990 report.

UNEXPECTED RESULT OF TUMOR SELECTIVITY RELATIVE TO PRIOR ART

11. Nothing in the prior art (of which I am aware) suggested that the double deletion could enhance the tumor specificity of vaccinia virus.

12. I have reviewed the three papers cited in McCart et al. 2001 on p. 8751, col. 2, ¶ 3 for the proposition that the combined effect of TK and VGF deletions on tumor specificity should be synergistic: McCart et al., Gene Ther 7: 1217 (Jul 2000), Puhlmann et al., Cancer Gene Ther 7: 66 (Jan 2000), Gnant et al., 230: 352 (Sep 1999). They were all published AFTER the May 1999 filing date.

13. I have also reviewed the papers cited in McCart et al. 2001 on p. 8754, col. 2, ¶ 1 to support an explanation for the tumor selectivity of the double deletion. The date-appropriate references cited in this section have only to do with a hypothetical mechanism of the VGF deletion and do not propose tumor selectivity.

14. There was no reason to expect that the double deletions would have the specific and targeted effect of attenuating the virus specifically for normal tissues relative to tumor tissue.

15. McCart et al. 2001 cited <u>no</u> pre-filing date publications to support the conclusion that the combination of a TK deletion and a VGF deletion would provide enhanced tumor selectivity.

16. The rationale for choosing the TK and VGF mutations was specific and incisive, not a random combination of safety mutations. At the time of the May 1999 filing date, there was no suggestion from the prior art to combine references to achieve a combined effect on tumor selectivity. The double deletion produces a new and unexpected result of tumor selectivity that is different from the results of the prior art.

NOT OBVIOUS BASED ON COMPARISON WITH CITED PRIOR ART

17. Mastrangelo et al. (1995) WO 95/31105 is confusing because on the one hand the *intent* seems to be to use vaccinia recombinants expressing cytokines in order to achieve *immuno*therapy or to use vaccinia infection as an adjuvant to boost host immunity to tumors, while on the other hand in practice several of the examples deal with direct exposure, by intravesical application or direct injection, of tumors with vaccinia virus in a fashion that could

result in direct killing of the injected tissue by the virus. In any event, although the PCT International Application intends to use vaccinia to treat cancer, nowhere does it deal with the invention of a vaccinia virus that may be administered systemically and that works by selective replication in tumor tissue as a result of specific engineering of genes that bias the tropism of the virus toward replication in growing cells and not in resting cells.

18. Dorner et al. U.S. Patent No. 6,103,244 describes a specific method of making vaccinia recombinants that is not used by the McCart et al. application, nor does the McCart et al. application deal with these specific methods of making vectors. The Dorner patent also makes no specific claims as to the use of the engineered vectors, in particular it makes no reference to cancer therapy.

19. Buller et al. 1988: I have already dealt with this one previously; paragraphs 5 and 6, above.

20. Whether considered singly or together, no motivation to select the claimed combination is taught by these references. Just because one CAN make a combination does not make the resultant combination obvious. These references do not suggest the desireability of combining the TK and VGF safety mutations to achieve reduced virulence, because, as discussed above, a prior art <u>double</u> deletion was merely comparable in replication to the single deletion and only the deletion of <u>multiple</u> virulence genes provided a highly attenuated effect. Moreover, considering the size of the prior art genus of virulence genes, the number of combinations was so large that one would <u>not</u> be educated towards the claimed combination.

THE SHOWING OF SYNERGISM

21. We first need to define synergy, and it is noteworthy for future arguments that the definition is somewhat ambiguous. According to the Oxford English Dictionary synergy means: "Joint working, co-operation." According to the American Heritage Dictionary synergy means: "The interaction of two or more agents or forces so that their combined effect is greater than the sum of their individual effects." The former definition seems to include effects that are simply additive. The latter definition points to effects that are greater than the sum of the parts. I use the latter definition.

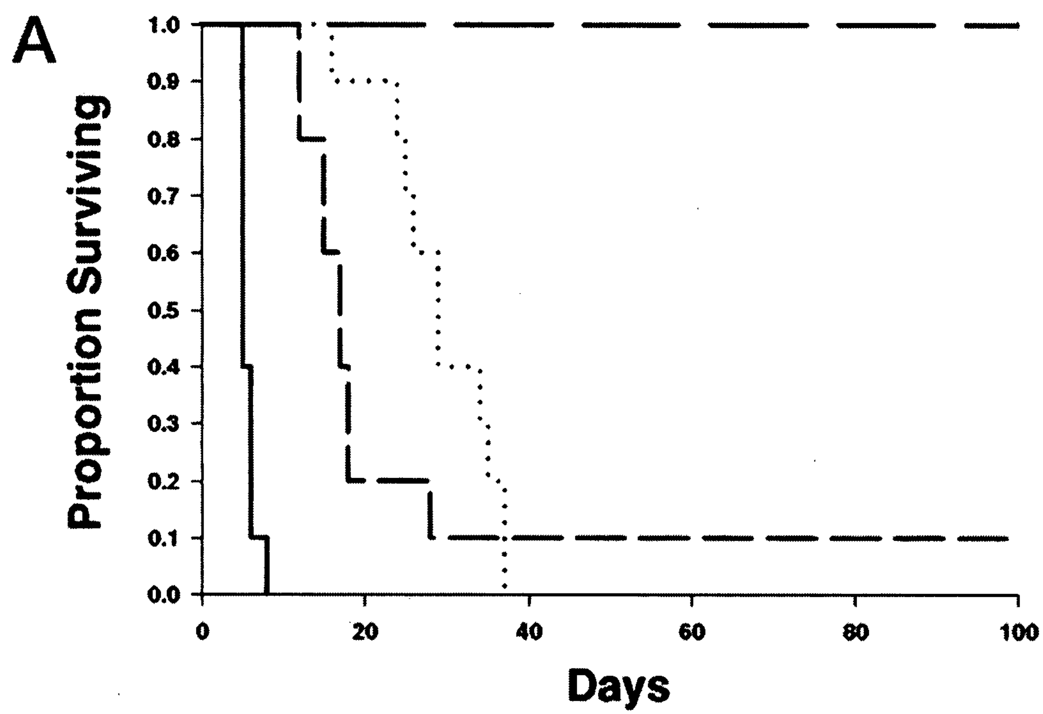

Fig. 4. *A*, survival of nude mice after treatment with 10^8 pfu of replicating WT (F13L+, *solid line*), TK- (VJS6, *dotted line*), VGF- (VSC20, *medium dash*), or vvDD-GFP (*long dash*) by i.p. injection ($n = 10$).

22. I believe that synergism has been demonstrated in McCart et al. 2001, specifically in Fig. 4A, for pathogenicity in animals. Four curves are shown, one for WT (solid line), one each for the single deletions of TK (dotted line) and VGF (medium dash), and one for the double mutant (long dash). The experiment describes the mortality of mice with respect to time after infection with a single dose of each virus. Comparing the curves, if the effects of the mutations were simply additive, I might have expected to see some mortality from the doubly deleted virus, e.g., a curve with a shallower slope relative to the single deletions. Instead, no mortality is seen, arguing that the double deletion is less virulent than would be expected simply from an additive effect of the single deletions.

Table 1 Median viral recovery from nude mouse tissues

Median (range) viral pfu/mg total protein of tissues 8 days after infection with WT (F13L+), TK- (VJS6), VGF- (VSC20), or vvDD-GFP. Nude mice (n = 3–5) were infected with 10^7 pfu of virus. On day 8 after infection, tissues were harvested and homogenized, and a standard plaque assay was performed.

	WT	TK-	VGF-	vvDD-GFP
Brain	2.8 (2.4–4.9) x 10^{4a}	1.3 (.21–20) x 10^2	1.5 (.76–4.3) x 10^2	0 (0–8)[a]
Liver	3 (.8–11)	7 (.6–13)	1 (.24–1.1)	0.1 (0–.2)
Spleen	5.1 (.59–21) x 10^2	12 (6–16)	23 (16–308)	8 (0–16)
Testes[b]	54 (0.4–2800)	12 (0.13–24) x 10^2	0.6 (0.4–0.8)	6.8 (0.7–28)
Bone marrow	1.0 (.08–10) x 10^4	3.0 (.075–7.6) x 10^3	1.1 (.41–2100) x 10^3	5.0 (0–12) x 10^2
Ovary	7.1 (2.6–9.7) x 10^6	9.3 (2.3–15) x 10^6	2.1 (.41–3.9) x 10^7	8.6 (.6–172) x 10^6
Tumor	17.0 (1.2–14) x 10^6	4.6 (.3–6.6) x 10^6	2.3 (.05–2.6) x 10^7	6.5 (.4–6.5) x 10^6

[a] $P = 0.011$.

[b] Testes samples obtained in a separate experiment.

23. Interestingly, one can argue from Table 1 that the effects of the mutations on *replication* are not synergistic but rather additive. In Table 1, the TK mutation reduces the virus titer in brain by 100 fold and the VGF mutation reduces the virus titer in brain by 100 fold. One would therefore predict that the combination of the two would reduce the titer in brain by 10,000 fold, that is, a 100 fold reduction (TK) reduced an additional 100 fold (VGF). In fact, the double deleted virus shows a 10,000 fold reduction in virus titer in brain, an additive effect (although a synergistic effect would not have been detected because the reduction in virus titer was to zero).

24. Similarly, the TK mutation reduces the virus titer in bone marrow by three fold and the VGF mutation reduces the virus titer in bone marrow by ten fold. One would therefore predict that the combination of the two would reduce the titer in bone marrow by 30 fold, that is, a three fold reduction (TK) reduced an additional ten fold (VGF). Indeed, the double deleted virus shows a twenty fold reduction in virus titer in bone marrow, close or even less than an additive effect.

25. In contrast, all four viruses were equally infective in tumor. The conclusion is that the combined effect on tumor selectivity, measured in terms of virus *replication*, was additive. Therefore, especially given some preliminary data like this, I would not have predicted a synergistic effect of the double deletion on *survival*.

26. We are left with the unique idea that a synergistic effect on *mortality* can result from an additive effect on virus *replication* in individual organs. One explanation of this might be that this additive effect on replication reduces the virus load below some critical threshold important in the more complex issue of overall mortality. Thus we see synergy for survival.

27. Consequently the experiments actually may reveal how subtle the concept of combined mutations or synergy is when dealing with engineered virus mutations. The lesson is that synergy would not have been predicted, yet it did occur.

SO-CALLED ADMISSION

28. I would also like to address the patent office's contention that by using the word "synergy", the authors made an admission. This usage could simply be a construction of

hindsight. However it is equally likely that, given the ambiguity in definition of the word synergy noted above, that they meant simply an additive effect rather than true synergy.

CONCLUSION

29. In conclusion, at the time of the May 1999 filing date, as a person of ordinary skill in the art, possessed with the knowledge reflected in the references, and motivated by the general problems faced in the art, I would <u>not</u> have been led to make the invention.

THIRD PARTY SIGNATORY

30. I have been retained as a consultant by McCart et al. and have no ownership interest in the McCart et al. patent application referenced above that is the subject of this examination. McCart et al. is paying me the normal hourly rate charged by me for my consulting services in this area of my expertise.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Respectfully submitted,

Dated: 9/25/06

By: Richard C Condit
Richard C. Condit, Ph.D.

AMEND

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EDUCATION

Institution	Degree	Year Conferred	Major Field
Yale University	Ph.D.	1975	Molecular Biophysics and Biochemistry
Univ. of Calif., Santa Cruz	A.B.	1970	Biology

RESEARCH AND PROFESSIONAL EXPERIENCE

1990-Present: Professor, Department of Molecular Genetics and Microbiology, University of Florida, Gainesville, Florida. Research on vaccinia virus biochemical genetics.

1998: Associate Dean for Graduate Education, College of Medicine, University of Florida, Gainesville, Florida.

1984-1990: Associate Professor, Department of Biochemistry, State University of New York at Buffalo. Research on vaccinia virus biochemical genetics.

1986-1987: Visiting Scientist (12 month sabbatical leave), Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Laboratory of Dr. Philip A. Sharp. Research on nonsense suppression and mammalian virus genetics.

1978-1984: Assistant Professor, Department of Biochemistry, State University of New York at Buffalo. Research on vaccinia virus biochemical genetics.

1977-1978: Postdoctoral, Department of Microbiology, State University of New York at Stony Brook. Advisors: Drs. Joseph Kates and William Bauer. Initiated research on vaccinia virus

1975-1977: Postdoctoral, Department of Molecular Virology, Imperial Cancer Research Fund, London, England. Advisor: Dr. Robert I. Kamen. Research on polyoma virus transcription.

1970-1975: Graduate Research, Department of Molecular Biophysics and Biochemistry, Yale University. Advisor: Dr. Joan A. Steitz. Research on regulation of gene expression during bacteriophage T7 infection. Thesis title: "Regulation of late gene expression in Bacteriophage T7".

FELLOWSHIPS

1975-1977: NIH postdoctoral fellowship awarded from the National Cancer Institute for postdoctoral research at the Imperial Cancer Research Fund in London, England.

1986-1987: NIH senior fellowship awarded for sabbatical leave at the Massachusetts Institute of Technology.

PROFESSIONAL SERVICE

Vice chair then Chair, Program committee, American Society for Virology (2001-2005)
Chair, DNA virus division, American Society for Microbiology (2001-2002)
FDA site visit review of CBER program (1997)
Editorial board, Journal of Virology, (1990-present)

Editorial board, Virus Research, (1990-2001)
Associate editor, Virology (1988-present)
Member, NIH virology study section (1990-1993)
Study section site visit for the Experimental Virology Study Section of NIH (1986)
Chairman, Poxvirus/Iridovirus Workshop, Cold Spring Harbor New York (1986)
Co-chairman, Poxvirus/Iridovirus Workshop, Madison, Wisconsin (1984)

PUBLICATIONS

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14. Pacha, R.F. and R.C. Condit (1985) "Characterization of a Temperature-Sensitive Mutant of Vaccinia Virus Reveals a Novel Function which Prevents Virus-Induced Breakdown of RNA", J. Virol. 56: 395-403.

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21. Hooda-Dhingra, U., C.L. Thompson, and R.C. Condit (1989) "Detailed Phenotypic Characterization of Five Temperature Sensitive Mutations in the 22 Kilodalton and the 147 Kilodalton subunits of the vaccinia virus DNA-dependent RNA polymerase" J. Virol., 63: 714-729

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28. Meis, R.J., and R.C. Condit, (1991) "Genetic and molecular biological characterization of a vaccinia virus gene which renders the virus dependent on isatin-§-thiosemicarbazone (IBT)" Virology, 182: 442-454.

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57. Prins C, Cresawn SG, Condit RC. (2004) "An isatin-beta-thiosemicarbazone-resistant vaccinia virus containing a mutation in the second largest subunit of the viral RNA polymerase is defective in transcription elongation." J Biol Chem. 279:44858-71.

58. Nollens HH, Gulland FM, Hernandez JA, Condit RC, Klein PA, Walsh MT, Jacobson ER (2006) Seroepidemiology of parapoxvirus infections in captive and free-ranging California sea lions Zalophus californianus. Dis Aquat Organ. 69:153-61.

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INVITED REVIEWS

1. Condit, R.C., and E.G. Niles (1990) "Orthopoxvirus Genetics" in Current Topics in Microbiology and Immunology (R.W. Moyer and P.C. Turner, eds.), 163: 1-39, Springer-Verlag, New York.

2. Condit, R.C., and E.G. Niles (2002) "Regulation of viral transcription elongation and termination during vaccinia virus infection", Biochim. Biophys. Acta 1577: 325-336

3. Condit RC, Moussatche N, Traktman P. In a nutshell: structure and assembly of the vaccinia virion. (2006) Adv Virus Res.;66:31-124.

BOOK CHAPTERS

1. Condit, R.C. (2001) "Principles of Virology" in Field's Virology, 4th edtion, DM Knipe and PM Howley, eds., Lippencott, Wilkins & Williams, Philadelphia

2. Condit, R.C. (2001) "Principles of Virology" in Fundamental Virology, 4th edtion, DM Knipe and PM Howley, eds., Lippencott, Wilkins & Williams, Philadelphia

3. Moyer, RW and Condit, RC (2005) "Poxviruses" in Topley & Wilson's Microbiology & Microbial Infections, 10th edition, BWJ Mahy and V ter Meulen, eds., Hodder Aronold, London

4. Marennikova, SS, Condit, RC, and Moyer, RW (2005) "Vaccinia Virus" in Orthopoxviruses Pathogenic for Humans, Shchelkunov, SN, Marennikova, SS, and Moyer, RW, Springer, New York

6. Condit, R.C. (2006) "Principles of Virology" in Fundamental Virology, 4th edtion, DM Knipe and PM Howley, eds., Lippencott, Wilkins & Williams, Philadelphia *in press*

5. Condit, R.C. "Poxviruses" in "Fundamentals of Molecular Virology" by N Acheson, John Wiley & Sons, (chapter complete, book still in preparation)

GRANTS

Active:

<u>4/04 – 3/09</u> NIH "Vaccinia Virus Genetics and Morphogenesis" $1,125,000 (direct costs)

<u>5/03 - 4/08</u> NIH; "Vaccinia Virus Biochemical Genetics" $1,250,000 (direct costs)

Past:

10/78 - 10/79 Biomedical Research Support Grant awarded through SUNY,Buffalo; "Temperature Sensitive Mutants of Vaccinia Virus" $7,500 (direct costs)

11/79 - 11/81 NSF; "Temperature Sensitive Mutants of Vaccinia Virus" $90,000 (total costs)

9/81 - 8/84 NIH; "Vaccinia Virus Biochemical Genetics" $208,176 (direct costs)

9/84 - 8/87 NIH; "Vaccinia Virus Biochemical Genetics" $275,594 (direct costs)

2/84 - 2/87 NSF; "Genetic and Physical Map of Vaccinia Virus Hind III D Fragment" $225,000 (total costs); R. Condit as co-investigator, E. Niles as principal investigator.

2/87 - 2/90 NSF; "Genetic and Physical Map of Vaccinia Virus Hind III D Fragment" $240,000 (total costs); R. Condit as co-investigator, E. Niles as principal investigator.

9/87 - 3/93 NIH; "Vaccinia Virus Biochemical Genetics" $774,133 (direct costs)

5/93 - 4/98 NIH; "Vaccinia Virus Biochemical Genetics" $821,406 (direct costs)

5/98 - 4/03 NIH; "Vaccinia Virus Biochemical Genetics" $1,084,970 (direct costs)

10/01 - 9/02 ATCC "Maintain collections of living reference strains of microorganisms" $20,000 (total costs)

PROFESSIONAL MEMBERSHIPS

American Society for Virology (charter member)
Federation of the American Society of Experimental Biology
American Society for Microbiology